BEFORE THE BOARD OF APPEALS AND INTERFERENCES
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Serial No. 09/165,460

Applicants: Rine et al.

Filed: Nov 3, 1998

Docket No. B96-021-3

Title: *AFC1 and RCE1: Isoprenylated CAAX Processing Enzymes*

Customer No. 23379

Confirmation No. 7914

Group Art Unit: 1652

Examiner: Ramirez, D

CERTIFICATE OF MAILING
I hereby certify that this corr. is being deposited with the US Postal Service as First Class Mail in an envelope addressed to the Comm. for Patents, Washington, D.C. 20231 on Mar 5, 2005

Signed _____
Richard Osman

REPLY BRIEF

The Honorable Board of Appeals and Interferences
United States Patent and Trademark Office
Washington, D.C. 20231

Dear Honorable Board:

This Reply Brief is responsive to the Examiner's Answer dated Feb 25, 2005.

I. THE EXAMINER'S REJECTION OF CLAIMS 31 and 39 UNDER 35USC103(a) IS IMPROPER.

We worry that the substantive issue is this appeal is getting eclipsed by a largely irrelevant dispute over exactly what information was presented in particular historical Genbank entries. Empathically, we have always presumed (and encourage the Board to presume) that the prior art includes the sequence of the entire yeast genome, and innumerable computer predictions of potential open reading frames (ORFs) throughout the genome, including the sequences cited by the Examiner. We further agree that given the cited computer-predicted ORF, a properly motivated artisan could make and use the claimed expression vectors with a reasonable expectation of success. It is only at the "properly motivated" part where we absolutely part company.

SEQ ID NOS:1 & 3 are the inherent sequences of natural Afc1 and Rce1 transcripts,

which have long existed in nature. Afc1 and Rce1 genomic sequences have also been previously discovered by humans as part of whole-genome sequencing projects. As we have repeatedly pointed out, the entire yeast genome was largely sequenced at the time this invention was made. Whether or not a portion of the yeast genome including AFC1 was sequenced prior to our filing date is of no consequence, because their sequences, as part of the complete genomic sequence, are merely an inherent aspect of that genome. The invention derives from identifying and characterizing two genes in isolation from the genome, and this record provides no evidence that the claimed sequences were previously isolated, characterized or in any way identified apart from gross yeast genomic sequence.

The Rose et al. database entries indicate that they were data collected by the Munich information center for protein sequences (MIPS) on behalf of the European yeast chromosome X sequencing project. Similarly, the Lye et al. entries indicate that they were data collected for the Saccharomyces cerevisiae chromosome XIII sequence project. Both studies involved sequencing entire yeast chromosomes, and the associated entries, as originally submitted to Genbank, and as properly relied upon by the Examiner, were no more than machine-predicted open-reading frames of raw genetic sequence. These original entries anticipate or render obvious expression vectors of isolated yeast genes little more than does the source yeast chromosome.

Of course, the database entries as recovered by the Examiner include annotations identifying the genes and their functions, *as determined by the present Applicants*. Armed with this information, the entries provide motivation to create expression vectors. Without this information, the entries provide a list of every machine-construed prospective ORF of the yeast chromosome. The Examiner identified and isolated the cited sequences from this vast, inherent set of machine-construed ORFs only by using our disclosed sequences as probes. Without the benefit of our disclosure, what would direct one skilled in the art to these particular machine-nominated ORFs, and invest the time and money required to make the claimed expression vectors?

Prior to our disclosure, there was no known ORF for Afc1. What existed was raw or machine-construed genomic sequence which included Afc1 sequence among vast genomic

sequence. Here, the relevant ORFs were made know by the Applicants, and the annotations of the genomic databases were subsequently updated to reflect Applicants's disclosure. There is no evidence of record, and there will never be any evidence of record, that someone other than the Applicants provided motivation to isolate and express the natural sequence encoding Afc1.

Raw genomic sequence has long been subject to annotation from machine (computer) postulation of candidate genes, transcription factor binding sites, regulatory elements, etc. Machine reading parameters rely on simple pattern probability assessment, and may be arbitrarily adjusted to nominate arbitrarily more or fewer regions (see, e.g. Lye et al., discussed below). That is why even when entire genomes are sequenced, we get wildly different "guesstimates" of how many genes might be there, depending on which "gene-finder" program is used, and even with the same program the results vary wildly depending on what assignment stringencies are used. The human genome has been long since sequenced and subject to countless machine interpretations - yet try to find three biologists who will agree on how many ORFs there are in the human genome. Without Appellants disclosure, the skilled artisan would have had no idea whether the cited particular computer-predicted ORF in fact encodes any protein, or whether it is a "dubious ORF"[1], an "ELF"[2], a pseudogene, or an endogenous retrovirus or transposon, etc.

The Examiner may not use Applicant's functional determination to go back to genomic sequence and pick out one postulated sequence among innumerable false-negatives and false-positives. Repeatedly underlining her allegation that she is "in no way using Appellants' functional characterization of the Afc1 protein as motivation to make the claimed invention" (e.g. Answer, p.12, lines 5-6) does not make it true – that is exactly what she is doing, for

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[1] "Dubious ORFs" is a disparaging term of art for apparently meaningless computer-predicted ORFs; which are not conserved in other *Saccharomyces* species and for which there is no experimental evidence that a gene product is produced in S. cerevisiae. Many ORFs classified as "Dubious" are small and overlap a larger ORF of the class "Verified" or "Uncharacterized"; however, overlap with another ORF does not mandate that an ORF be classified as "Dubious." See, http://www.yeastgenome.org/help/glossary.html.

[2] "ELFs", which stands for "Evil Little Fellows" is an even more disparaging term of art for apparently biologically meaningless computer-predicted ORFs (Ochman 2002, Trends Genet. 2002 Jul;18(7):335-7).

without Appellants' functional characterization, where is practical motivation?

The Examiner repeatedly underlines her contention that one skilled in the art is "highly motivated to characterize and determine the biological role of a yeast ... protein...." (e.g. Action, p.10, lines 5-6). That allegation is both true and irrelevant. Of course a skilled yeast biologist is motivated to characterize and determine the role of all yeast proteins – that is what they do for a living. But that is not at issue here. The issue here is whether that biologist would have been motivated to clone and express a particular computer-predicted ORF without any functional guidance whatsoever. It is one thing to be motivated to know what every yeast protein does; it is an entirely different thing to be motivated to clone and express a particular computer-predicted ORF without any functional guidance whatsoever.

According to the Examiner, a computer-predicted "potential ORF would have been sufficient to highly motivate one of skill in the art to make the claimed vectors and transform host cells with such vectors in order to produce enough protein for *characterization studies*...." (Answer, p.12, lines 7-9). And exactly what "characterization studies" might those be? Exactly what is this skilled person going to do with this polypeptide of which she has no knowledge of its function, or where, when, how, or even if it is expressed? The artisan can only subject the polypeptide to characterization studies, e.g. particular binding assays, if she already knows what the protein does. Otherwise, what is she to do with it; sprinkle it on some yeast cells to see if anything happens?

The reason yeast biologists characterize protein function through functional genomics is because functional genomics provides tools for manipulating protein expression in the cell so that a meaningful readout might be obtained. That is how gene function is invariably determined. The fact of the matter is that without the functional information provided by Appellants, the artisan has no use for the expressed polypeptide, and hence no motivation to make it.

II. THE EXAMINER'S REJECTION OF CLAIMS 35, 37-38, 43 and 45-46 UNDER 35USC103(a) IS IMPROPER.

Here again, the issue is not whether SEQ ID NOS:1 & 3 are in the prior art. Again, we

have always presumed (and urge the Board to similarly presume) that the prior art includes the sequence of the entire yeast genome, and innumerable computer predictions of potential open reading frames (ORFs) throughout the genome, including the sequences cited by the Examiner. We also agree that given the cited computer-predicted ORF, a properly motivated artisan could make and use the claimed expression vectors with a reasonable expectation of success.

SEQ ID NOS:1 & 3 are the inherent sequences of natural Afc1 and Rce1 transcripts, which have long existed in nature. The entire yeast genome had been largely sequenced prior to the filing of our patent application, including the identification of thousands of computer-predicted ORFs (many of which are now characterized as dubious ORFs or ELFs, supra). What Lye discloses are computer predictions of thousands of possible coding sequence (CDS) regions. A computer is programmed to input raw genomic sequence, select all possible CDS regions over 100 codons, and then exclude those that are more than 50% overlapped by a larger predicted CDS. The authors promise that CDS regions of the initial dataset subsequently eliminated by the algorithm are nevertheless "available upon request." In addition, the disclosure provides algorithm-predicted PROSITE database matches, though the authors caution that some of these may be "fortuitous".

Lye does not disclose any gene or gene product, but the results of a first run effort to sequence the entire XIII chromosome of Saccharomyces cerevisiae. That natural yeast XIII chromosome is, of course, prior art, and Lye provides no more than an inherent property of that chromosome - its sequence. Lye discloses no more than raw genomic data weighted by a computer for thousands of possible genes and genetic elements. The Examiner uses our own disclosure to select out one of these and uses our own disclosure to provide motivation to recombine it in an expression vector. In the absence of any evidence for function, there would have been no motivation to select out one of the thousands of yeast ORFs of unknown function, isolate what may or may not be a coding sequence, and operatively join it to a promoter in an expression vector, as expressly required by our claims.

The Examiner may not use Applicant's functional determination to go back to genomic sequence and pick out one postulated sequence among innumerable false-negatives and false-positives. Repeatedly underlining her allegation that she is "in no way using Appelants'

functional characterization of the Rce1 protein as motivation to make the claimed invention" (e.g. Answer, p.16, lines 10-11) does not make it true – that is exactly what she is doing, for without Appelants' functional characterization, where is practical motivation?

The Examiner repeatedly underlines her contention that one skilled in the are is "highly motivated to characterize and determine the biological role of a yeast ... protein...." (e.g. Action, p.15, lines 23-24). That allegation is both true and irrelevant. Of course a skilled yeast biologist is motivated to characterize and determine the role of all yeast proteins – that is what they do for a living. But that is not at issue here. The issue here is whether that biologist would have been motivated to clone and express a particular computer-predicted ORF without any functional guidance whatsoever. It is one thing to be motivated to know what every yeast protein does; it is an entirely different thing to be motivated to clone and express a particular computer-predicted ORF without any functional guidance whatsoever.

According to the Examiner, a computer-predicted "potential ORF would have been sufficient to highly motivate one of skill in the art to make the claimed vectors and transform host cells with such vectors in order to produce enough protein for *characterization studies*...." (Answer, p.16, lines 14-15). Again, exactly what "characterization studies" might those be? Exactly what is this skilled person going to do with this polypeptide of which she has no knowledge of its function, or where, when, how, or even if it is expressed? The artisan can only subject the polypeptide to characterization studies, e.g. particular binding assays, if she already knows what the protein does. Otherwise, what is she to do with it?

In the abstract, the Examiner's argument sounds great: biologists like to know about protein function, here's a potentially encoded protein, so it would be obvious to make the protein because then we could study it, figure out if its real, and determine its function. Unfortunately, that analysis is divorced from the reality of how gene and protein function is and can be determined. That analysis ignores that fact that without some a priori knowledge of what the predicted protein does, there simply no functional characterization that can be logically performed on a completely blank protein, and no rational yeast biologist is going to go to the trouble of making a computer-predicted protein when she has nothing meaningful to do with it once she expresses it.

Absent a prior art suggestion that SEQ ID NO:1 or 3 encode a protein of determined function sufficient to motivate the isolation, cloning and expression of such SEQ ID NO using techniques such as those of the cited Nozaki et al. (US Pat No 4,997,767) and Sambrook, J. et al. (Mol. Cloning, Cold Spring Harbor Press, p. 16.3-16.16) references, the claims are in compliance with 35USC103(a).

Appellants respectfully request reversal of the pending Final Action by the Board of Appeals.

Respectfully submitted,
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